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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/060,188	04/14/1998	DOMINIC P. BEHAN		9333

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	PAPER NUMBER
1646	31

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/060,188	BEHAN et al
Examiner	**Art Unit**
Nirmal S. Basi	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 8, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *34, 40, and 45-76* is/are pending in the application.

4a) Of the above, claim(s) *71-74* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *34, 40, 45-70, 75, and 76* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Nov 13, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Response filed 8/8/02 (paper number 30) has been entered.

2. ***Election/Restriction***

Applicant's election without traverse of Group I, species 116 encompassing "Location:ventromedial hypothalamus, Correlated with Physiological Function: food intake", in Paper No. 26 (7/19/01)is acknowledged. Claims 33-34, 38-40 and 45-76 are pending. Newly added claims 71-74, in paper number 28 (entered 4/25/02, filed 4/10/02), will not be examined. Since applicant has received an action on the merits for the originally presented invention (Group I, method for identifying candidate compounds), this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 71-74, drawn to compound or pharmaceutical composition identified by the method claims 69, 70 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03

3. Applicant has requested clarification of corrected drawing, Figure 12. The corrected or substitute drawings with formalized version of Figure 12, filed November 13, 2000, was received by the Office and entered as paper number 20 on 2/5/02. The drawings is approved by the examiner.

4. The Declaration of Watson has been fully considered. The rejections under 35 U.S.C. 101 and 112, first paragraph, present in paper number 27 are withdrawn in view of

Applicants arguments, amendments and the Declaration of Watson filed in paper numbers 28 and 30.

Claim Rejection, 35 U.S.C. 112

5. Claims 34, 40, 45-70 and 75-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 61 and 62 are indefinite because it is not clear what is an endogenous sequence. The specification discloses the term endogenous means which is naturally produced by a mammal. It is not clear what parameter of the sequence determines if it as an endogenous sequence as compared with it not being an endogenous sequence. Further, since proteins can be mutated in nature as well by the hand of man, it is not clear which sequences would considered endogenous and how they could be differentiated. Cells produce many proteins, all naturally, it is not clear which would be considered endogenous as compared to those that are not endogenous. Similarly claims 69 and 70 are rejected for being indefinite for use of non-endogenous. Since the metes and bounds of endogenous cannot be determined it follows non-endogenous is also indefinite.

Claims 67 and 68 are indefinite because it is not clear what is an abnormal physiological function so as to allow the metes and bounds to be determined. Applicant argues one skilled in the art would readily understand that instant usage of the term "abnormal physiological function"

as referring to physiological functions linked or associated with diseases or disorders. Applicants arguments have been fully considered but not found persuasive. Applicant provides the example of sweating to address abnormal physiological function but does not provide any details as to how mush sweating has to occur for it be an abnormal physiological function, in conditions where extreme heat and physical exertion are not factors. Further, when is motility of stomach and intestines, ureter function, salivary secretion, uterine contraction contractility of heart muscle, mucosa volume, etc.(to name but a few examples from the physiological functions disclosed in claim 75) considered abnormal as compared to normal physiological function? At what magnitude of the response is the function considered abnormal. Therefore abnormal physiological function is not an absolute value in many cases, and without guidance form the specification the metes ad bound so the claim cannot be determined.

Claims 69, 70 and 75 are indefinite because it is not clear what is the correlation of the receptor to physiological function. Specifically what relationship of the receptor to function defines the correlation to a physiological function. Further is the correlation between the endogenous receptor or constitutively activated receptor and physiological function.

Claims 69 and 70 are indefinite because it is not clear what is a reporter signal and what it reports.

Claim 76 is indefinite because it is not clear what animal the compound is administered to. If the animal does not contain the GPCR under investigation then administering said

compound to a mammal will neither confirm a decrease or increase in physiological function. Further it is not clear how the decrease or increase in correlated with physiological function.

Claims 69 and 70 are rejected because it is not clear how a GPCR with an associated physiological function and no known endogenous ligand is subjected to constitutive receptor activation to create a constitutively activated GPCR.

Claims 34, 40 and 5-66 are reacted for depending on a indefinite base claim and fail to resolve the issues raised above.

New Matter rejection

6. Claims 75 and 76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants arguments and the Lewis declaration, pertaining to new matter, have been fully considered but not found persuasive. Applicant and the Lewis' disclosure argue that the broad disclosure of the originally filed patent application provides support for the claimed species. Applicants arguments and the Lewis declaration have been fully considered but not found persuasive. Claims recite in the preamble, "wherein a location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function". Claim 75 contains 147 locations of expression of receptor and correlated physiological functions. The afore mentioned location of expression of

receptor and correlated physiological functions do not appear in the original specification. Also the further step of claim 76 which states, "administering said compound to a mammal and confirming a decrease or increase in said correlated physiological function" does not appear in the original specification. Applicant argues based on the specification on page 34, lines 10-12, the concept of the receptor and function of claim 75 can be deduced. Applicants arguments have been fully considered but not found persuasive. The specification does not provide the receptors or their correlated physiological function. To overcome the rejection Applicant must provide evidence where specifically, in the specification, the subject matter of claims 75 and 76 is disclosed.

Claim Rejection, 35 U.S.C. 112

7. Claims 34, 40, 45-70 and 75-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of identifying a non-endogenous candidate compound as an agonist or an inverse agonist to an endogenous constitutively activated G-protein coupled receptor (GPCR), wherein a the location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function and wherein an endogenous ligand for said receptor has not been identified said method comprising contacting the non-endogenous candidate compound with said constitutively activated GPCR and identifying the compound by using the assays disclosed on pages 55-63 of the specification, wherein the GPCR is the is the constitutively

activated GPCR which causes cancerous growth in Kasposi's sarcoma, does not reasonably provide enablement for subjecting other GPCR, with no known ligand and associated physiological function to create constitutive activated receptors to be used in the methods of claims 34, 40, 45-70 and 75-76. The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 70, 40, 53-60, 64, 66, 68, 75, and 76 encompass a method of identifying a non-endogenous candidate compound as an agonist or an inverse agonist to an endogenous constitutively activated G-protein coupled receptor (GPCR), wherein a location of expression of said receptor in a mammalian tissue source is known and said receptor has been correlated with at least one mammalian physiological function. The specification discloses one constitutively activated GPCR which causes cancerous growth in Kasposi's sarcoma wherein an endogenous ligand for said receptor has not been identified. Although the specification contemplates other GPCR that can be used in the claimed method they are not disclosed. Therefore one species that meets the limitation of claims 70, 40, 53-60, 64, 66, 68, 75, and 76 is disclosed. Pertaining to claims 34, 45-52, 63-65, 67 there is no disclosure of GPCRs, with no known ligand, that are associated with a physiological function that can be constitutively activated to be used in methods of instant invention. There is no disclosure of how to predictably create constitutively activated receptors with an associated physiological function that cause at least a 30% difference in reporter signal.

Claim 75 discloses 147 locations and correlated physiological function but does not disclose a single receptor, with no known ligand that can be constitutively activated to provide a 30% difference in reporter signal in the assay claimed. Further the art recognizes that all GPCR, while sharing the seven transmembrane motif, have considerable variation in amino acid sequence. The constitutively activated mutations are not limited to the third intracellular loop and the critical site varies with each G-protein coupled receptor (See, Teitler et al, US Pat 6,255,089, ref A, column 4, lines 37-55). The complexity of constutively activation GPCRs is disclosed by Teitler, column 4, last paragraph, which shows that general approach can not be used to constitutively activate all GPCRs. The claims do no disclose how the receptors are constitutively activated. Although claims 45-62 provide further limitations on specific sequences of amino acids that must be present in the orphan receptor said sequences do not limit how the receptor is to constitutively activated. The specification discloses methods of activating GPCRS with known ligands, said GPCRs being limited to beta adrenergic receptors. There is no disclosure on how to constitutively activate receptors with no known ligand that have been associated with a physiological function. The specification discloses the use of the GPCR associated with Kaposi's sarcoma, said receptor is inherently constitutively active. There is no disclosure in the specification on the relationship of physiological function with other orphan receptor. Further, there is no indication that the constitutively activated receptor will have the same physiological function as the non activated receptor. Therefore ligands that bind one species (ie. constitutively activated) may not have the same effect as those that bind the other

species (i.e non-constutively activated). The specification does not disclose how to use the compounds that may be identified that have completely different effects on activated and non-activated receptors. Also since the method does not correlate the reporter signal with physiological function, the relationship between receptor and physiological is not disclosed, the compounds identified by instant method, while being agonists or antagonists, may have no effect on the physiological function of the native receptor. Applicant has not disclosed how to use the compounds identified by claimed method and do not have an effect on the physiological function. Further pertaining to claim 76 the specification fails to disclose production of mammal comprising the constutively activated GPCR or its use in a functional assay. If the animal does not contain the GPCR under investigation then administering said compound to a mammal will neither confirm a decrease or increase in physiological function. There is no disclosure of how the decrease or increase is correlated with physiological function.

Thus, in view of lack of specific guidance in the specification, the skilled artisan at the time of filing would be unable to use the claimed invention, in its full scope without undue experimentation. The quantity of experimentation required would include identifying an orphan GPCR, associating a physiological function to the orphan receptor, determine if it is constitutively active, or make a constutively active GPCR.

Claim Rejection, 35 U.S.C. 112

8. Claims 34, 40, 45-70, 75 and 76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to use of constutively activated GPCR with no known ligand and associated physiological function to be used to screen for agonists and inverse agonists. The specification discloses one constitutively activated GPCR which causes cancerous growth in Kasposi's sarcoma, where the endogenous ligand for said receptor has not been identified. No guidance is provided in the specification as to what minimal structural requirements are necessary for constitutive activation of GPCRs with no known ligand. There is the lack of representative number of species of GPCR with no known ligand and associated physiological function. There is lack of guidance on how to modify different families of GPCR to be constitutively active. It does not appear that Applicants were in possession of the genus of orphan receptors with an associated physiological function to be used in the claimed method at the time the invention was made. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). Even assuming high skill of the artisan, one could not predict the association of orphan receptor to physiological function or how to constitutively activate the vast number of differing GPCRs that are encompassed by the claims.

Claim Rejection under 35 U.S.C. 103

12. Claim 70 and 76 rejected under 35 U.S.C. 103(a) as being unpatentable over Gershengorn et al (US Patent 6,087,115, Ref B) in view of Cesarman et al. (US Patent 6,093,806, Ref C) and Teitler et al (US Patent 6255,089, Ref A). Gershengorn discloses method of identifying agonists and antagonists for constutively activated G-protein coupled receptors (GPCRs) by expressing in a host cell a constutively activated GPCR (GPCR of human herpes 8, known as Kasposi's sarcoma), exposing cell to test compound and measuring a reporter signal described above (see Abstract and Detailed Description of The Invention and claims),. Also contemplated is the administration of compound identified by the afore mentioned method to a subject to effect tumor formation or cell proliferation caused by GPCR associated with Kaposi's sarcoma. and disclosed is tumor formation or cell proliferation (column 5, lines 33-47). Gershengorn does not disclose a 30% difference in reporter signal. Cesarman et al discloses Kaposi's sarcoma protein and nucleotide. Teitler discloses the identification of agonist and inverse agonists to constutively activated GPCRs (see summary of the invention). Further, Teitler discloses the use of measuring reporter signal for constitutively activated GPCR activity, wherein the reporter signal is at least 30 % different compared with reporter signal in the presence of compound as compared with absence of compound, see Figures, especially Figure 21.

It would have been obvious for one of ordinary skill in the art to use the assay for identifying compounds to constitutively activated GPCR taught by Gershengorn to identify agonists and inverse agonists to constutively activated GPCR of Kaposi's virus taught by

Cesarman, and vary the reporter signal measured to indicate differences of up to 30% between signal induced by compound and absence of compound as taught by and Teitler. Further one of skill in the art would use the compounds identified by the afore mentioned assay and administer them to mammals to confirm a decrease in carcinoma. One would have been motivated to identify compounds by the above mentioned assay and administer them to a mammal because identification of agonists and inverse agonists is routine in the art and in instant case would provide compounds that could prevent tumor formation in Kaposi, sarcoma patients. Therefore, the claimed invention was obvious at the time of the invention.

Signed copies of the IDSs will be provided in the next Office Action

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
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